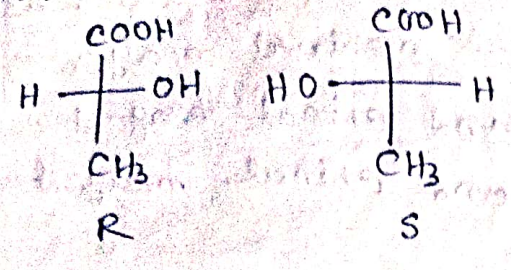
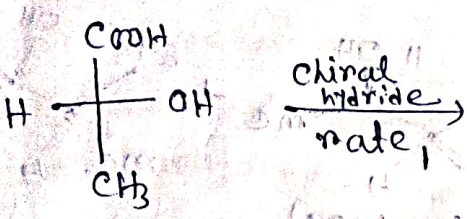
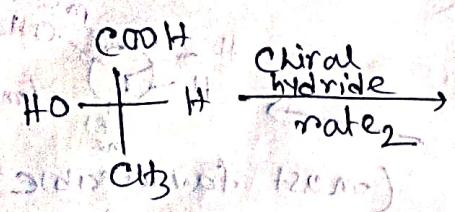
Asymmetric Synthesis :-



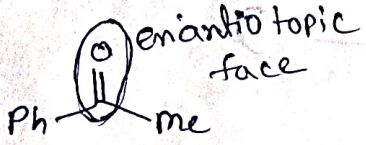
Enantiomers have same physical & chemical properties

Most of the physical & chemical properties of enantiomers are same. They only differ in optical rotation / activity & chemical reactions in chiral environment (like in our biological system)



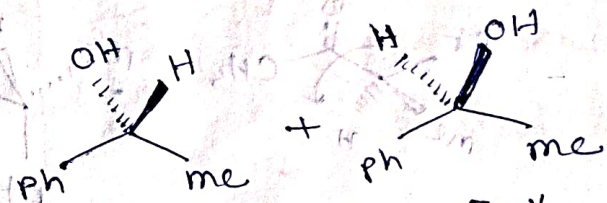


D(+) glucose ⫽ L(-) glucose



Acetophenone

Not an asymmetric synthesis.



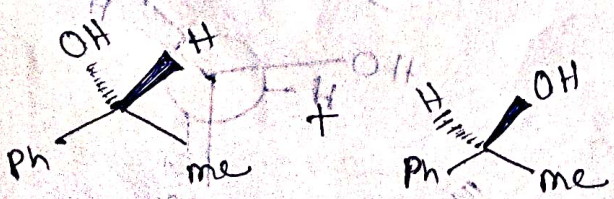
50 % 50 %

Racemic mixture.

[ee = 0]

Chiral catalyst
(S) - CBS + BH_3

asymmetric Synthesis.



R-alcohol major ~ 90%

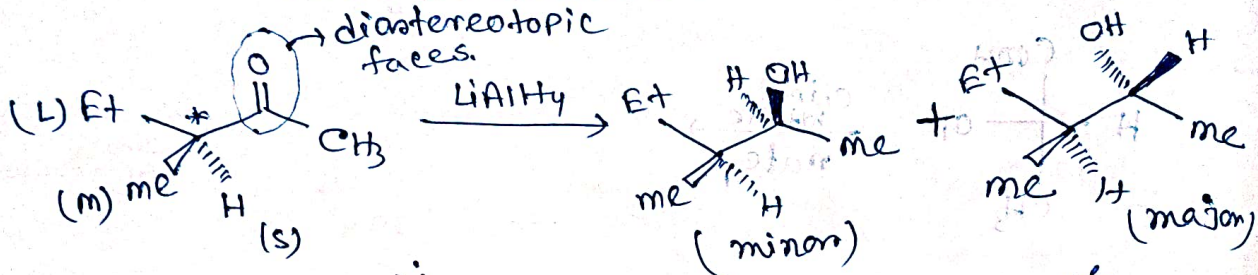
S-alcohol minor 10%

ee = 80%. [ee ≠ 0]

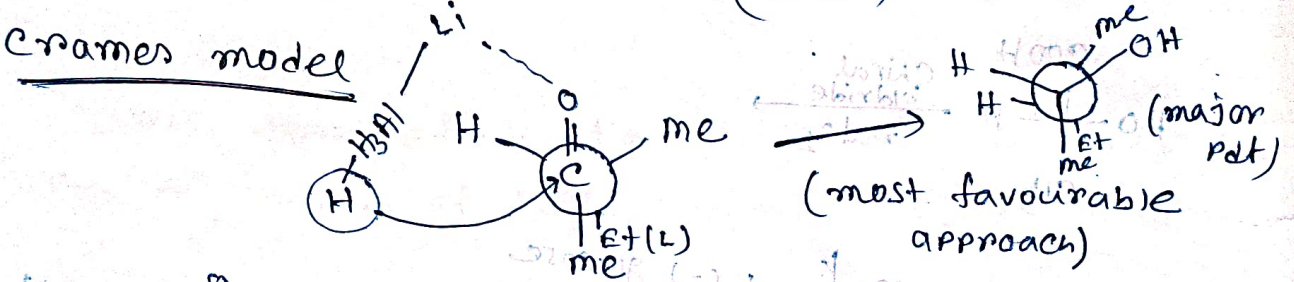
Different ways to carry out asymmetric synthesis

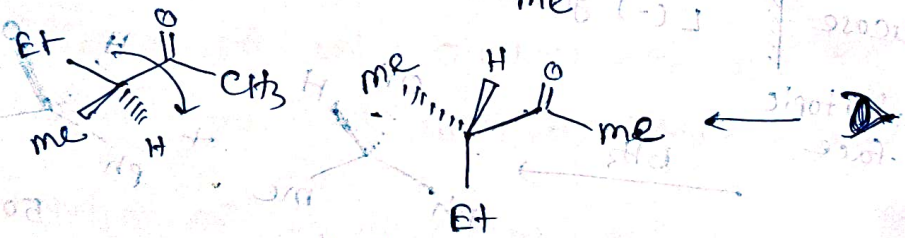
① using chiral substance & achiral reagent.
② using achiral substrate and chiral reagent
③ using chiral substrate and chiral reagent
④ using chiral catalyst
⑤ using chiral auxiliary
⑥ using chiral pool reagent.

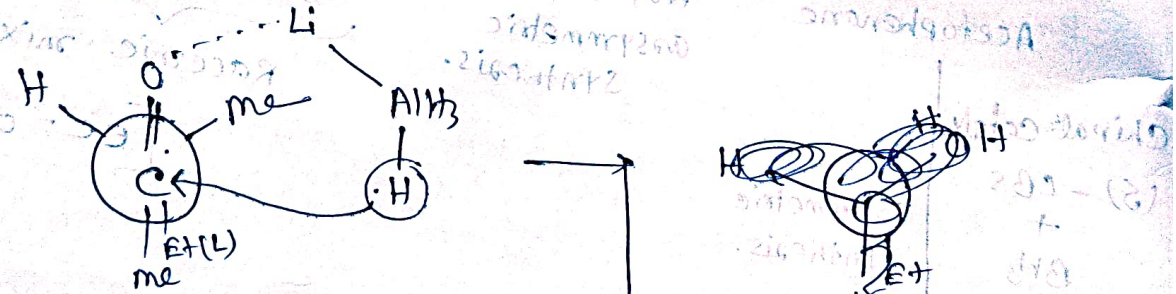
Using chiral substance and achiral reagent :-



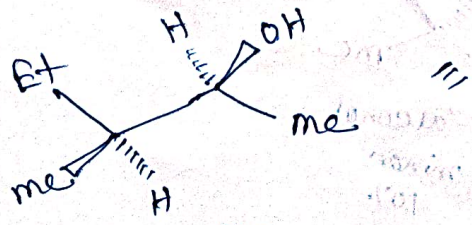
Cramer's model



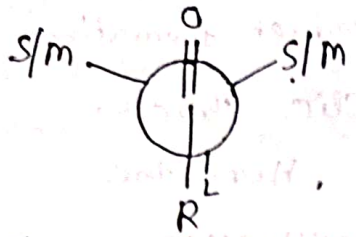




1 gr. Syn to $-\overset{\overset{O}{\|}}{C}$
↓
attack from medium size atoms.

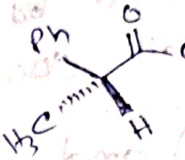


Crams model



most stable conformation

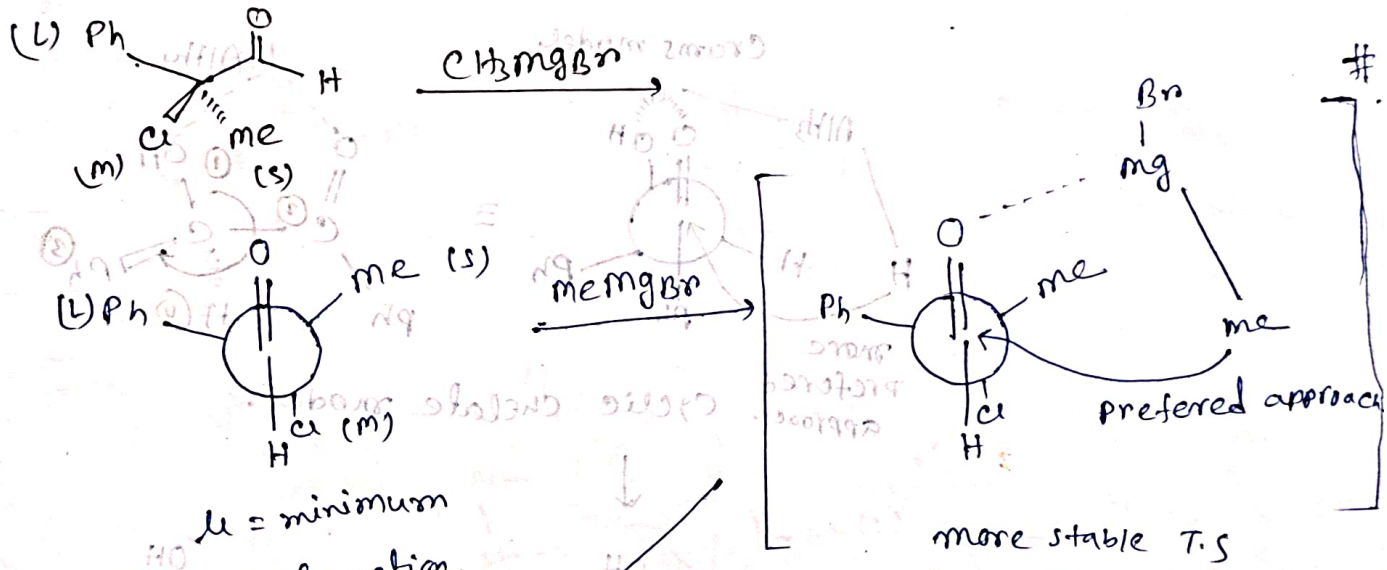
Q. predict the major and minor pdt when (R)-3-Phenyl-2-butanone is reduced LiAlH4, based on Cram's model. 2/3



Derivation from Cram's model :-

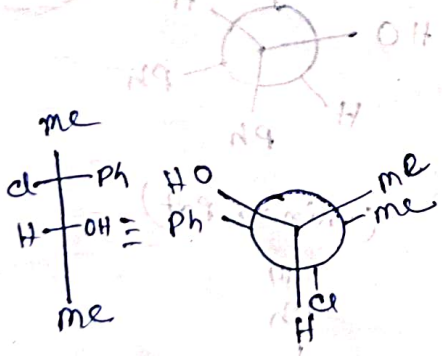
(1) If there is a halogen atom present at the chiral centre, then in order to minimize the dipole moment the halogen atom will be anti-periplanar w.r.to C=O. This is now the most stable conformation.

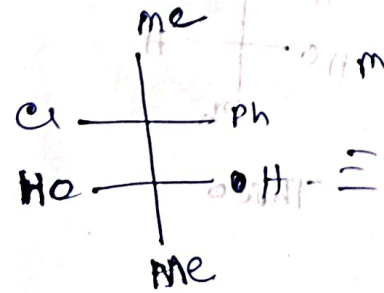
Q. predict the major and minor product when (S)-2-Chloro-2-phenylpropanal treated with CH_3MgBr.

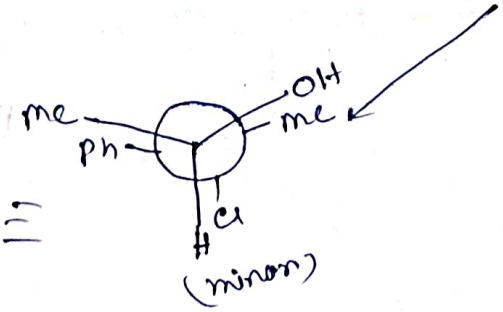


μ = minimum

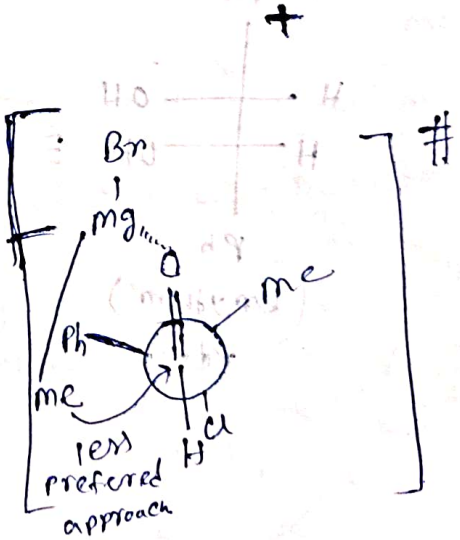
most stable conformation.







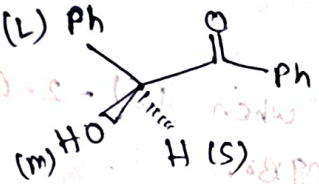
+

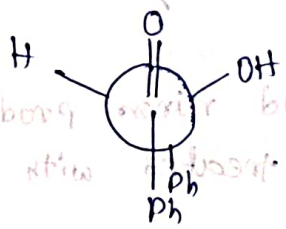


Less stable T.S.

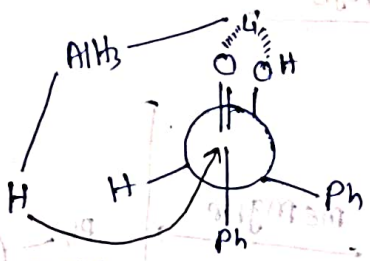
② If there present any chelating groups (like $-\ddot{O}H$, $-OR$, $-NH_2$, $-NHR$ etc) then the product formation can be correctely explained by 'cyclic chelate model' and by not by cram's model. Here the metal will coordinate with the carbonyl oxygen ($\overset{|}{C}=O$) and chelating group and will form a stable cyclic model.

(S)-Benzoin $\xrightarrow{LiAlH_4}$

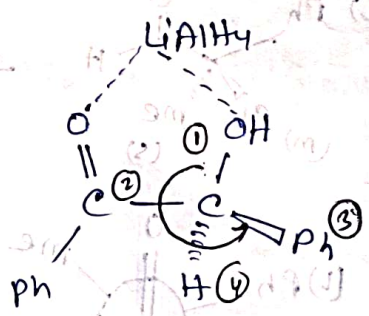




Crams model

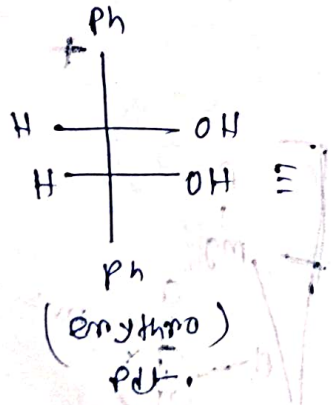


≡



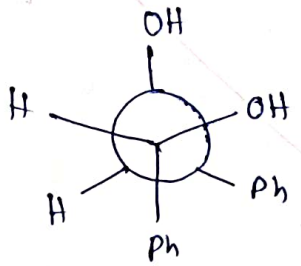
more prefered approach. Cyclic chelate model.

↓



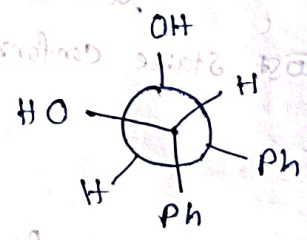
(erythro) pdt.

≡

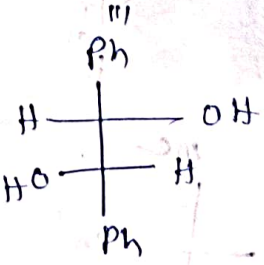


(major pdt)

+

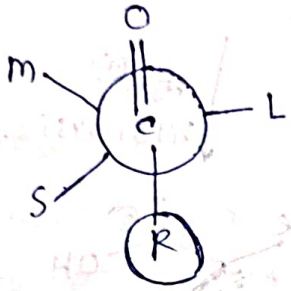


(minor pdt)

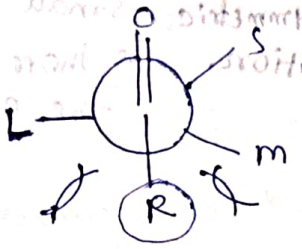


Threo

Felkin - Anh model :- According to this model the large group should be orthogonal (90°) w.r.to C=O group and the most stable conformation is that one where the -R group is flanked between L & S group.

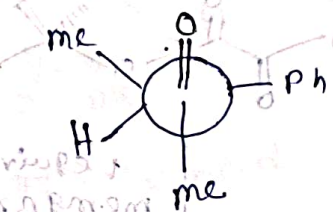


most stable Conformation

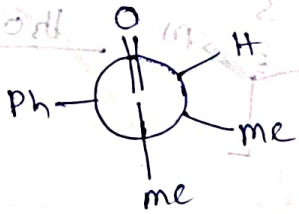


least stable Conformation.

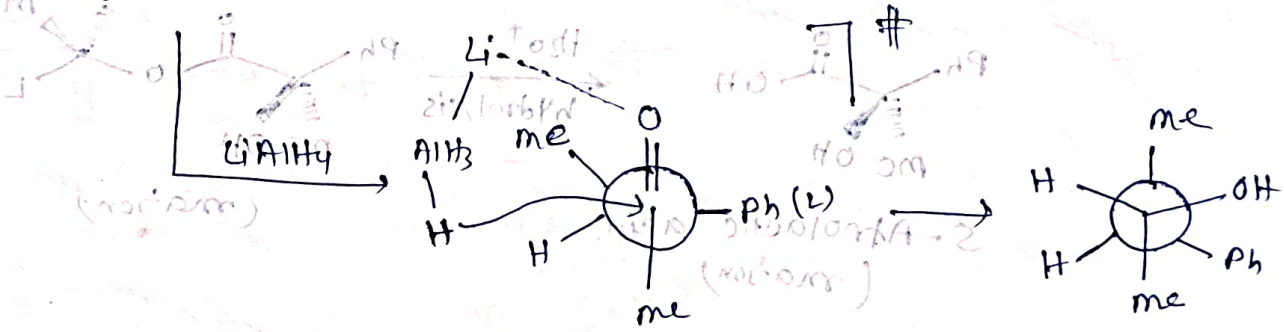
(9) predict the major and minor pdt when (R) - 3 - Phenyl - 2 - butanone is reduced with $LiAlH_4$ based on Felkin-Anh model.



(R) most Stable



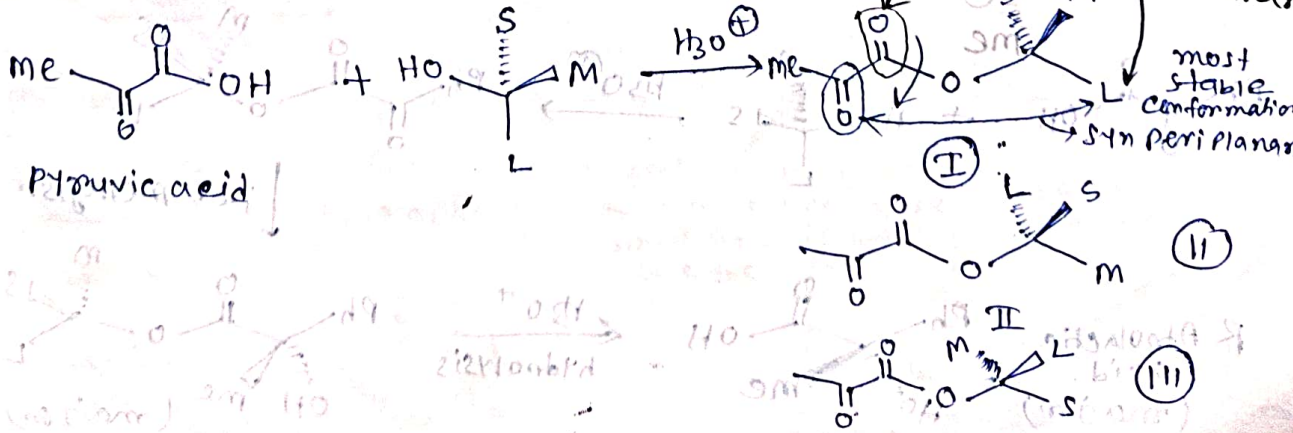
less Stable.

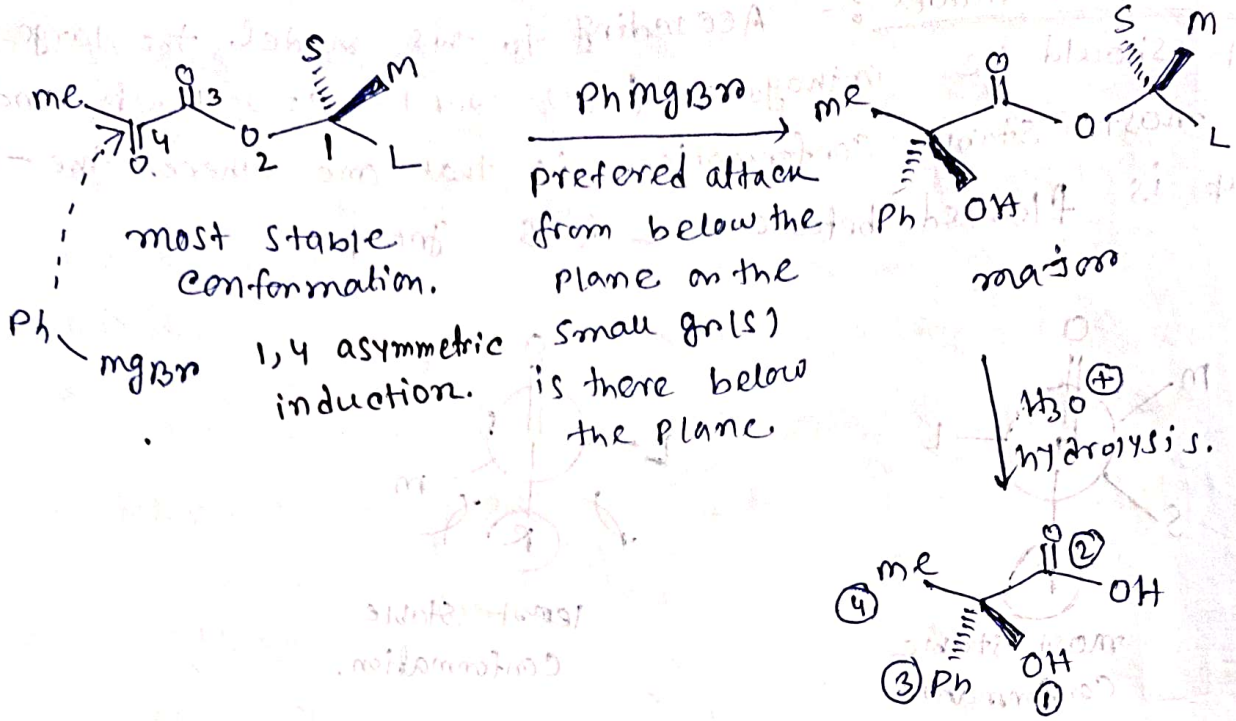


most Stable T.S

major product

Prelog's rule :- It is applied to determine the absolute configuration of an unknown alcohol :

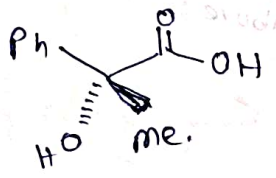



PhMgBr
most stable conformation.
1,4 asymmetric induction.
prefered attack from below the plane on the small gr(s) is there below the plane
major
H_3O^+ hydrolysis.
R-Atrolactic acid (major)
(S-2 octanol)
Benzoyl fumaric acid.
1 equiv. MeMgBr
S-Atrolactic acid (major)
(major)
R'-alcohol.
R Atrolactic acid (major)
(major)

α-Keto acid used	Grignard reagent	Configaration of alcohol	Configaration of major atrolactic acid
Pyruvic acid	PhMgBr	R-Alcohol	S-Atrolactic acid
Benzoyl fumaric acid	MeMgBr	R-Alcohol	R-Atrolactic acid.

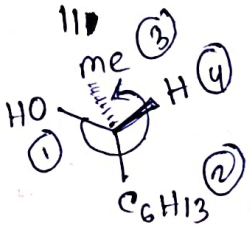
(Q) Find out the absolute configaration of a given 2-Octanol Sample when it ~~form ester with benzoyl formic acid~~ gives (R)-atrolactic acid as the major product after ~~form~~ formation of ester with benzoyl formic acid followed by reaction with MeMgBr.

Retrosynthetic analysis.



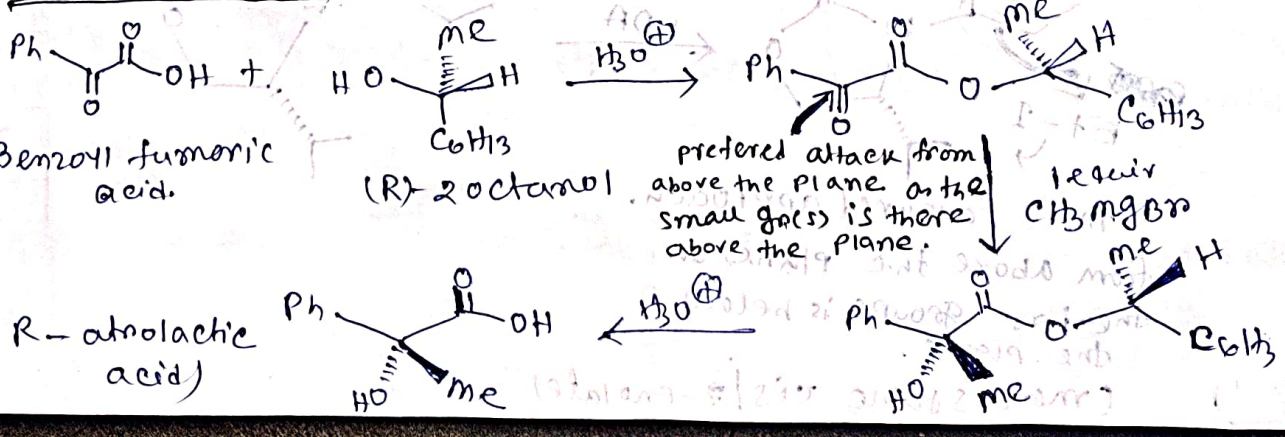
R-atrolactic acid.

Benzoyl fumaric acid.



(R)-Alcohol

forward reaction:



Benzoyl fumaric acid.

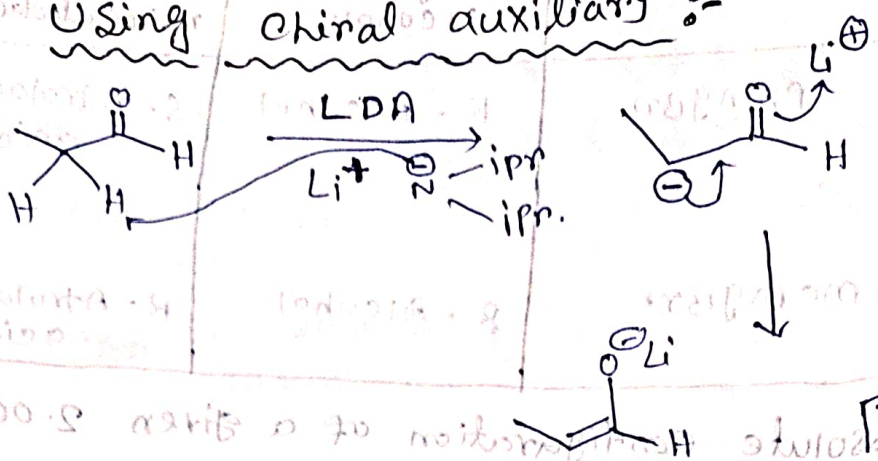
(R)-2 Octanol

preferred attack from above the plane as the small gp(s) is there above the plane.

I equiv CH_3MgBr

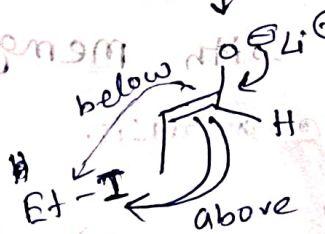
R-atrolactic acid)

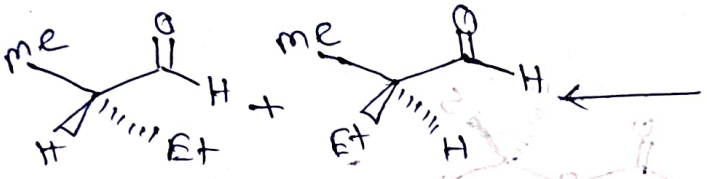
(v) Using chiral auxiliary :-



cis/Z-enolate (less stable)

trans/E-enolate (more stable)



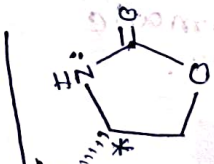


50% 50%

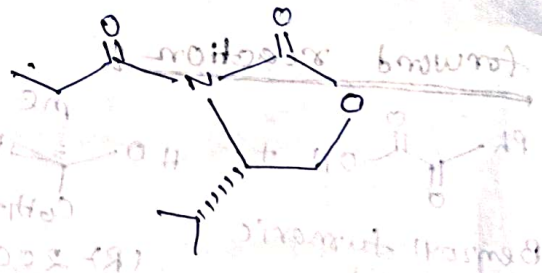
Racemic mixture.

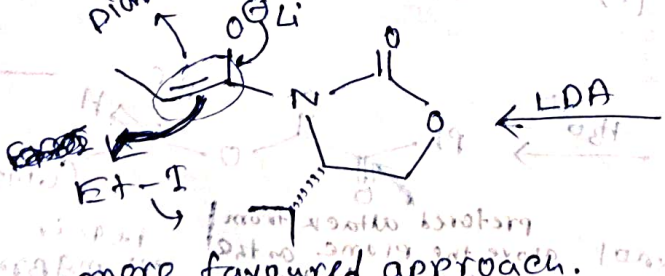
How to make it asymmetric (ee > 0)

That we can do with the help of chiral auxiliary.



2-oxazolidinone derivative



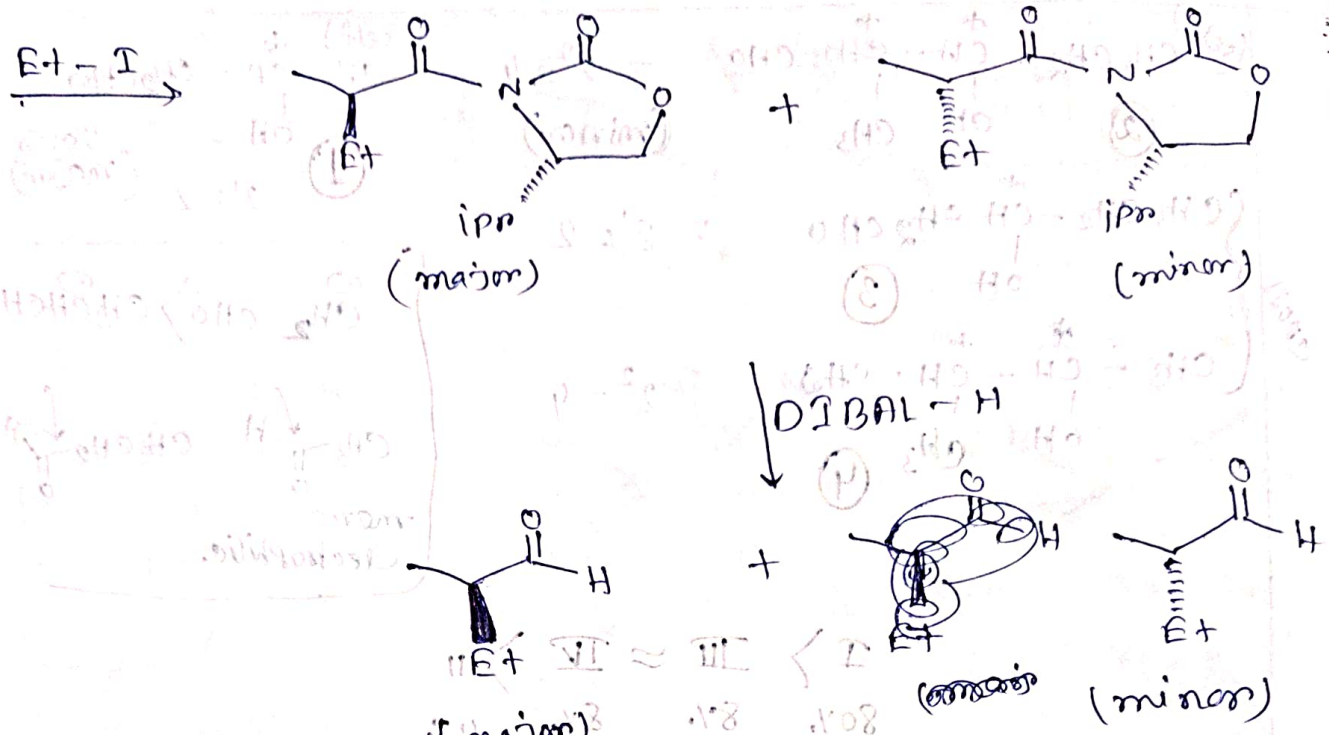


pro-stereotopic faces.

more favoured approach.

from above the plane on the -ipr groups, is below the plane.

(more stable cis/Z-enolate)



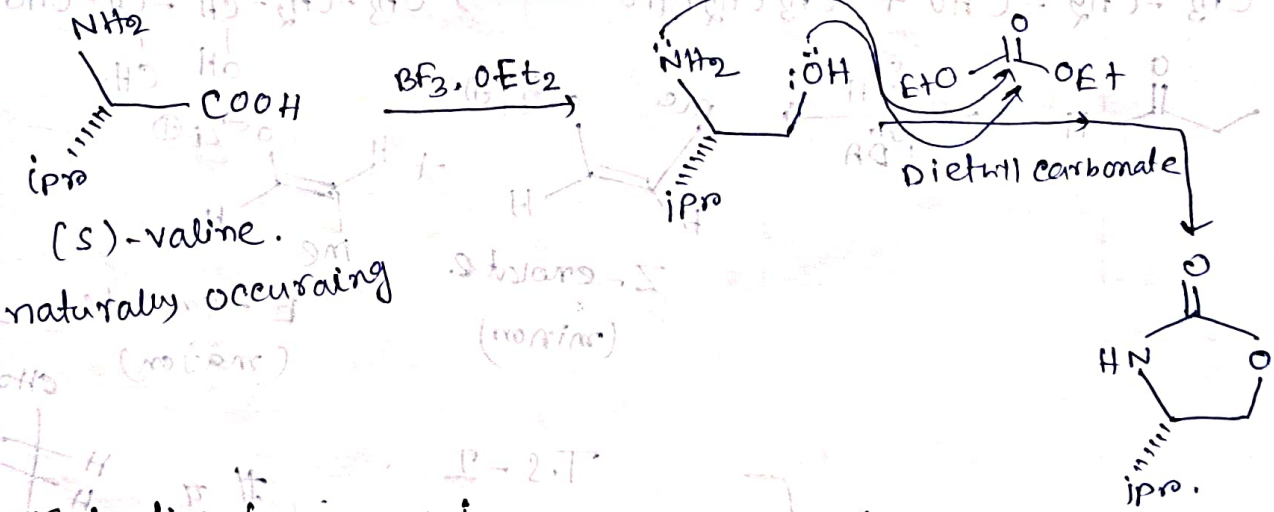
A + B ⟶ C not asymmetric

Racemic.

$A + R^* \longrightarrow A-R^* \xrightarrow{B} C-R^* \xrightarrow{-R^*} C$

ee > 0

non racemic.



Stereoselective / Asymmetric Aldol Condensation :-

$CH_3\overset{*}{C}HO \xrightarrow[2'-2]{NaOH \text{ or } H_3O^{\oplus}} CH_3-CH(OH)-CH_2CHO$ self aldol condensation

$CH_3CHO + CH_3CH_2CHO \xrightarrow{NaOH} CH_3-CH(OH)\underset{CH_3}{CH}-CHO + CH_3CH_2\underset{OH}{CH}CH_2CHO$

$CH_3-\underset{OH}{CH}-CH_2CHO + CH_3CH_2\underset{OH}{CH}-\underset{CH_3}{CH}-CHO.$

(self) $CH_3CH_2-\underset{OH}{\overset{*}{CH}}-\underset{CH_3}{\overset{*}{CH}}-CHO$ ② $= 2^2 = 4$ (minor)

(self) $CH_3-\underset{OH}{\overset{*}{CH}}-CH_2CHO$ ① $2^1 = 2$ (major) 50:50

Cross

$CH_3CH_2-\underset{OH}{\overset{*}{CH}}-CH_2CHO$ ③ $= 2^1 = 2$

$CH_3-\underset{OH}{\overset{*}{CH}}-\underset{CH_3}{\overset{*}{CH}}-CHO$ ④ $= 2^2 = 4$

$\overset{\ominus}{CH_2}-CHO > CH_3\overset{\ominus}{C}HCHO$

more electrophilic.

I > III ≃ IV > II

80% 8% 8% 4%

40% 40% 2% 2%

How to make only one aldol out of these 12 aldols or major product.?

$CH_3-CH_2-CHO + CH_3CH_2CHO \xrightarrow{dil\ NaOH} CH_3-CH_2-\underset{OH}{\overset{*}{CH}}-\underset{CH_3}{\overset{*}{CH}}-CHO$

$\xrightarrow[\text{or LDA}]{\overset{\ominus}{O}H}$

Z-enolate (minor)

+ E-enolate (major)

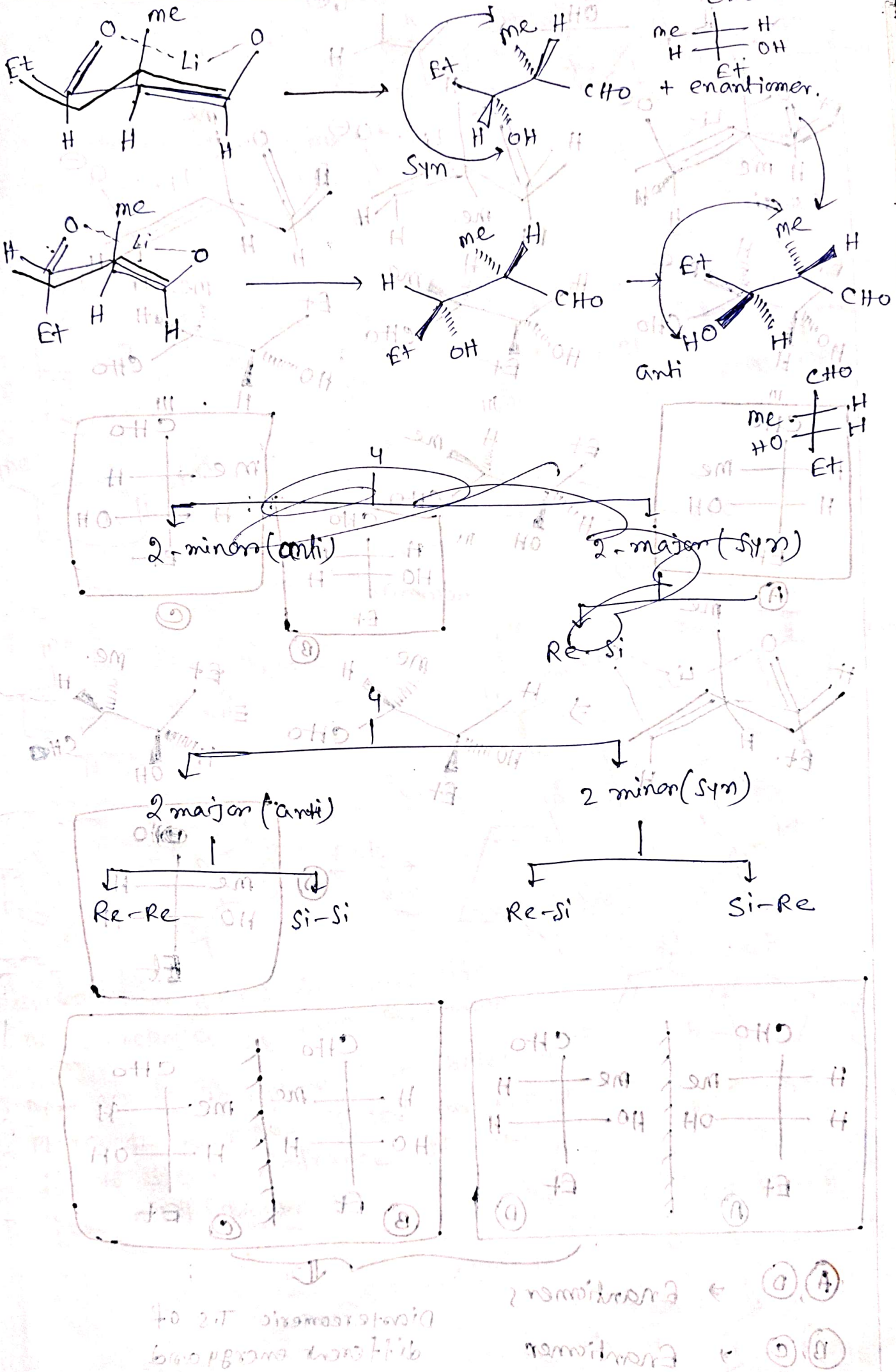
T.S-I

T.S-II

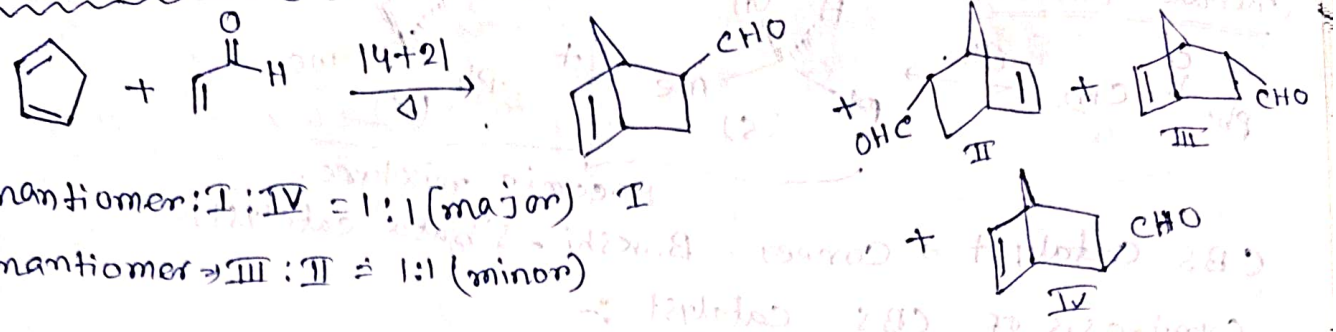
Re-Re combination.

Si-Si combination.

Ts-I & T.S-II are enantiotopic T.S

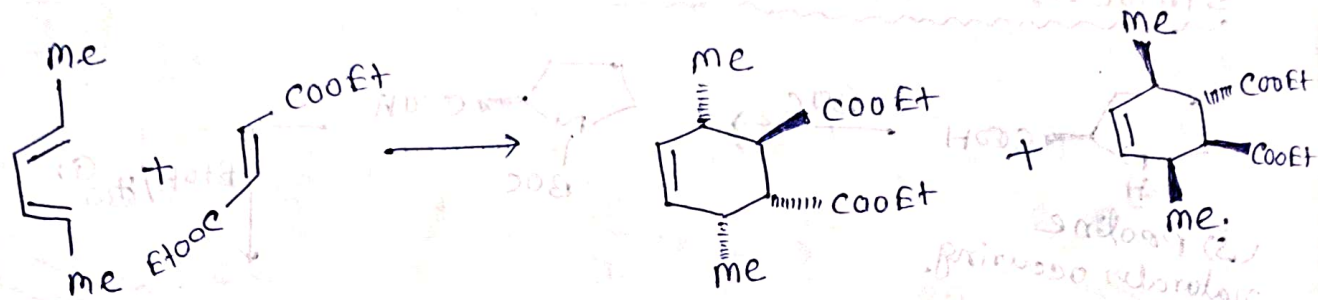

me
O
Li
O
Et
H
H
H
me H
Et
CHO
H
OH
Syn
CHO
me
H
OH
Et
+ enantiomer.
me
O
Li
O
H
Et
H
H
me H
H
CHO
Et
OH
me
H
Et
CHO
HO
H
Anti
CHO
me
H
HO
Et
4
2 minor (anti)
2 major (syn)
Re-Si
4
2 major (anti)
2 minor (syn)
Re-Re
Si-Si
Re-Si
Si-Re

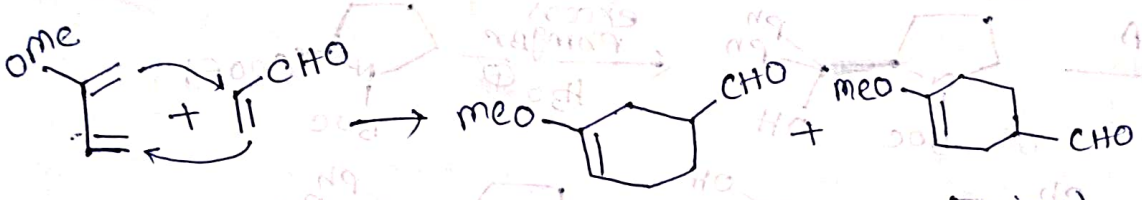
Assymetic Diels-Alder reaction :-

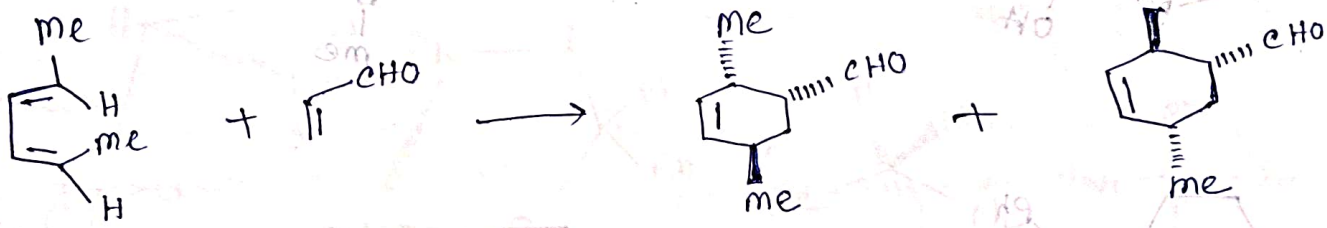


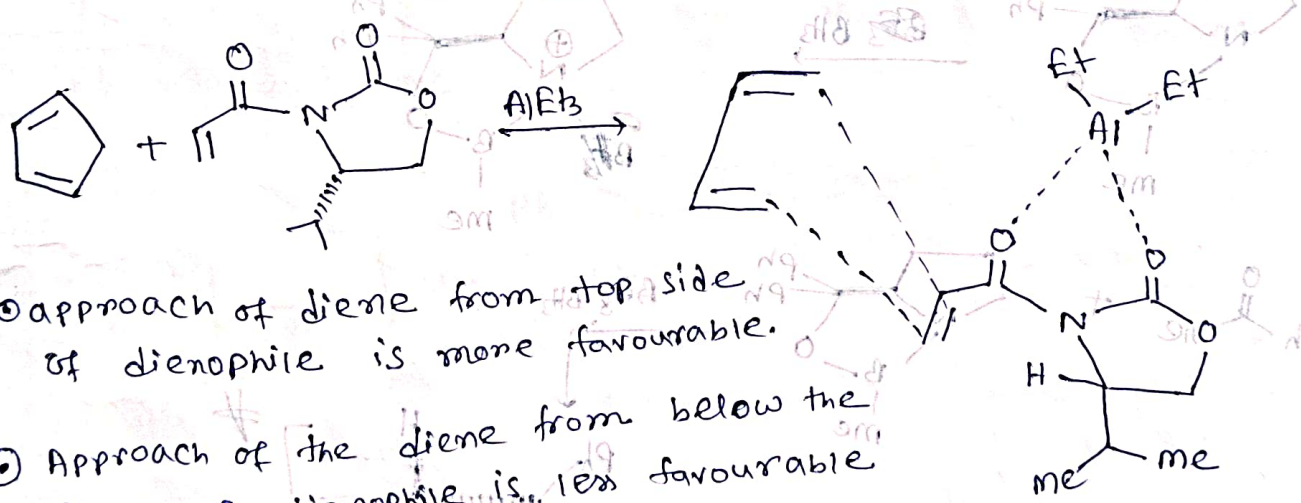
Enantiomer: I : IV = 1 : 1 (major) I

Enantiomer → III : II = 1:1 (minor)



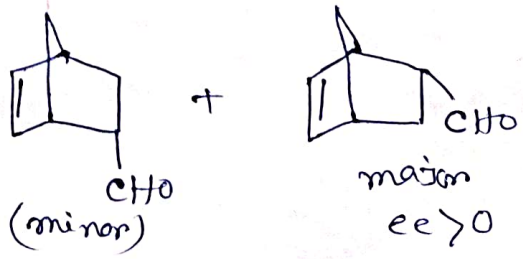




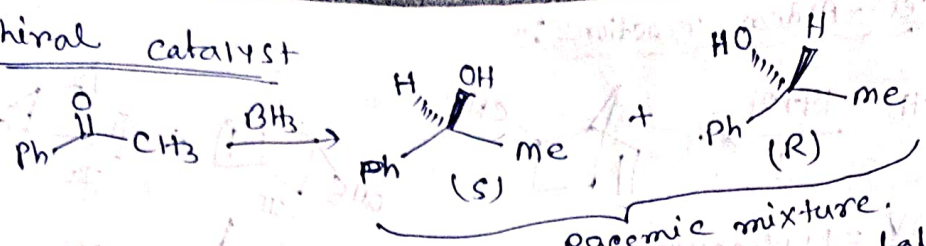


- ⊙ approach of diene from top side of dienophile is more favourable.
- ⊙ Approach of the diene from below the plane of dienophile is less favourable due to steric hindrance of the iso-propyl group.

DIBAL-H



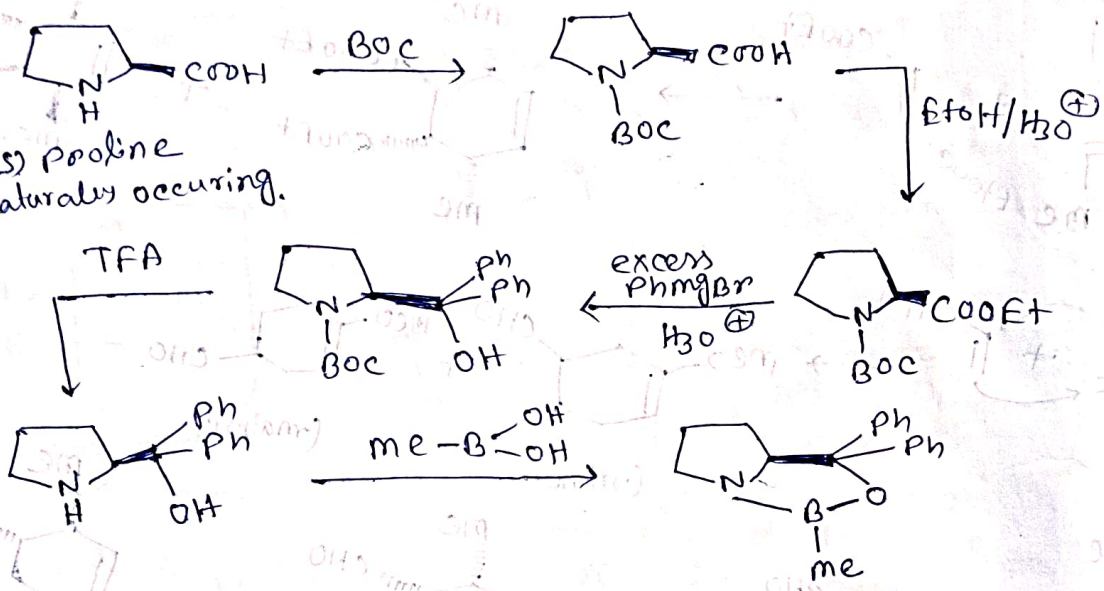
Chiral catalyst

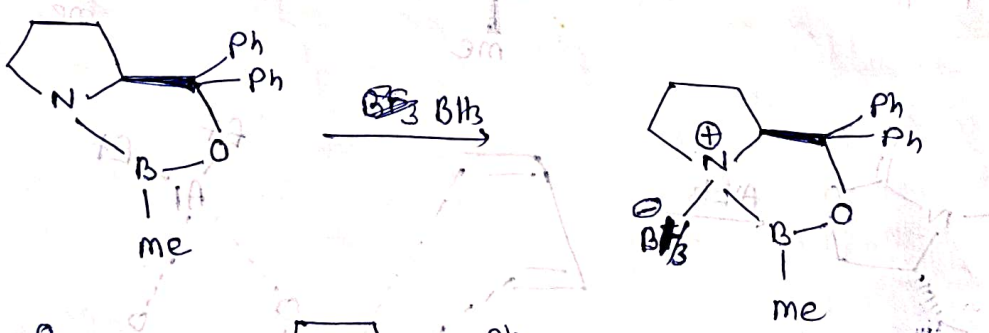


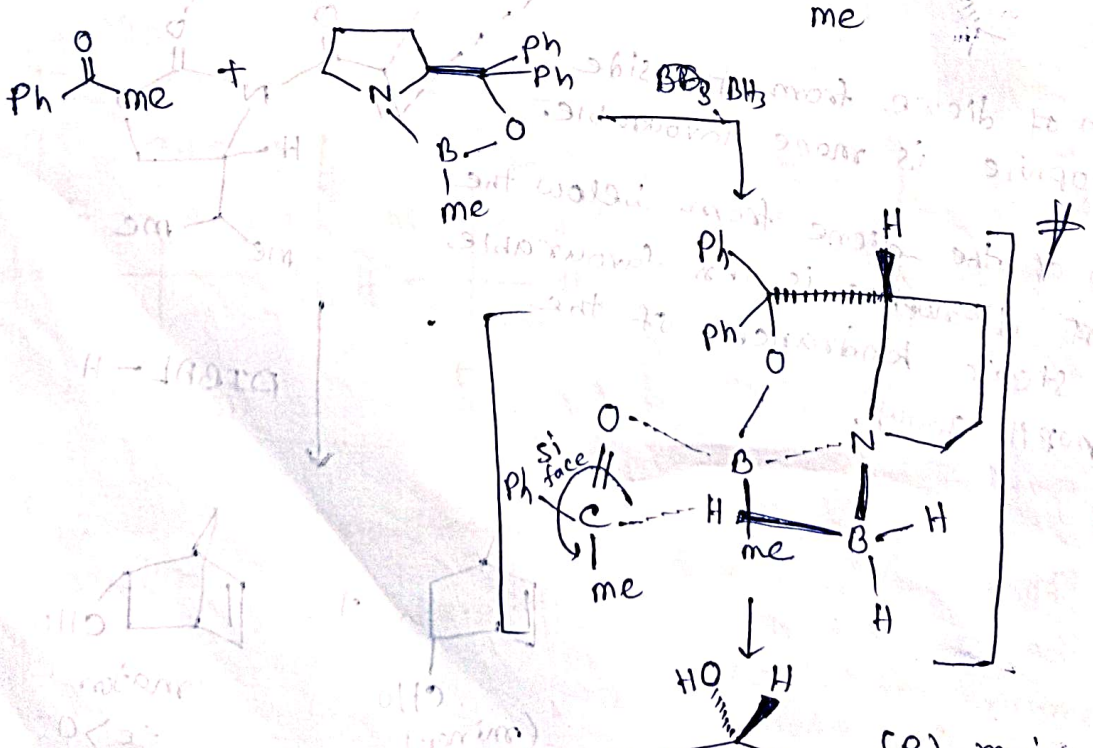
Racemic mixture.

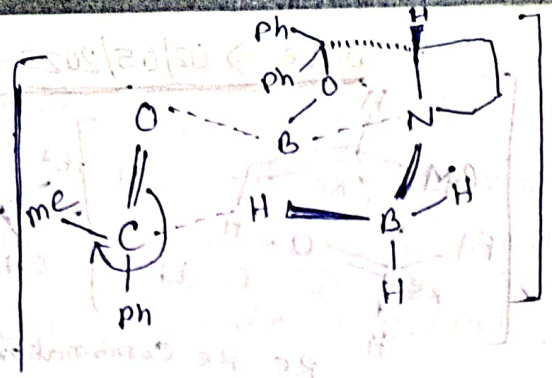
CBS Catalyst → Correy - Bakshi - Sibata catalyst.

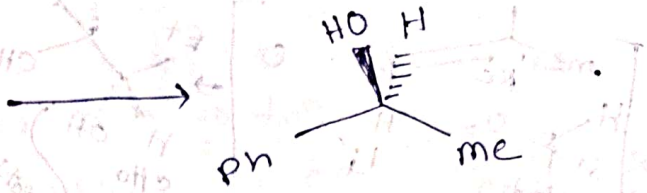
Synthesis of CBS catalyst :-



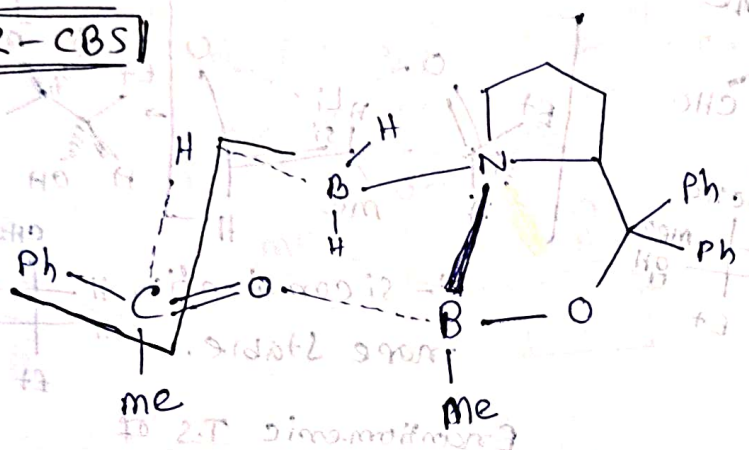


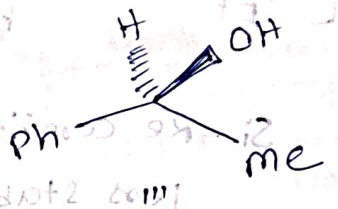


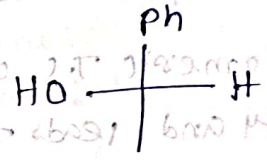


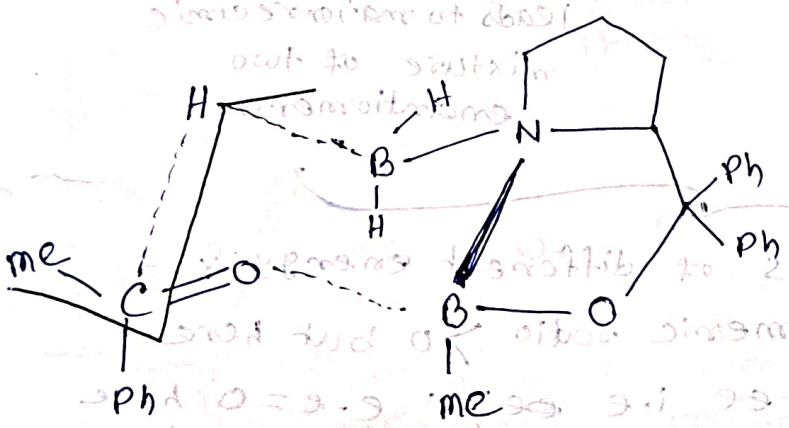


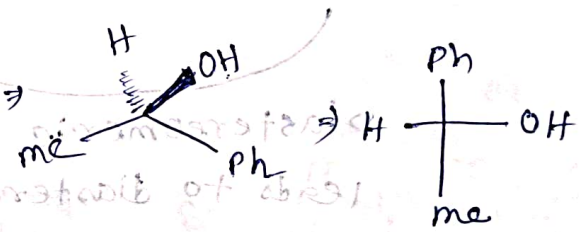
R-CBS

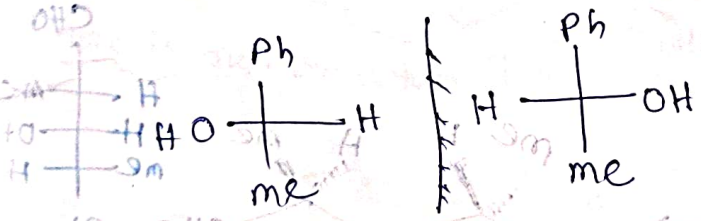




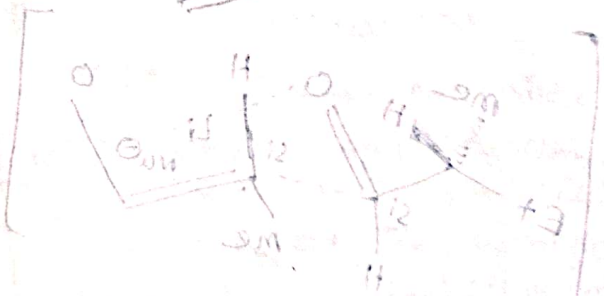


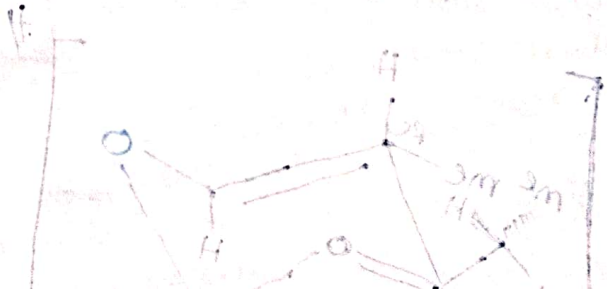




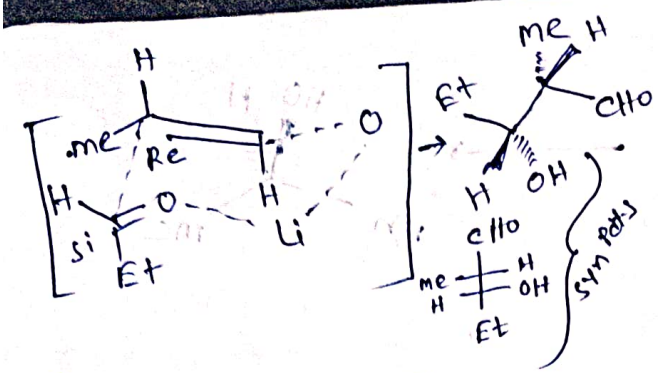


enantiomers,



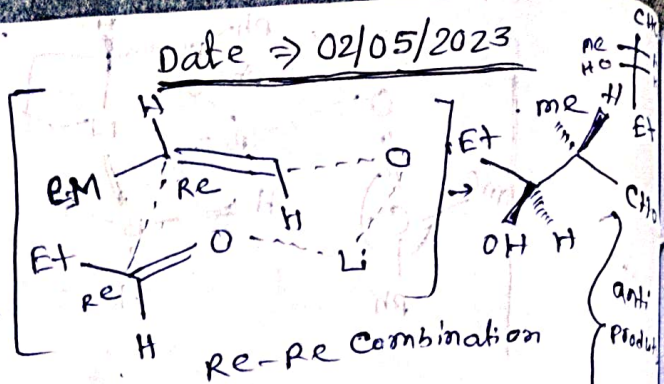


Date ⇒ 02/05/2023

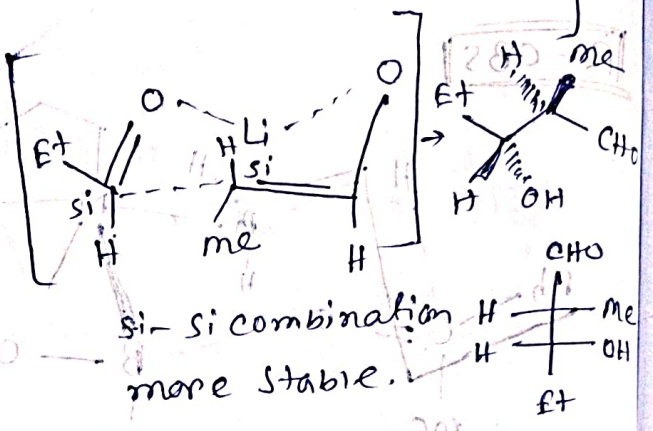


Si-Re combination
less stable

Enantiomeric T.S of equal energy and leads to minor recimic mixture of another pair of enantiomers.



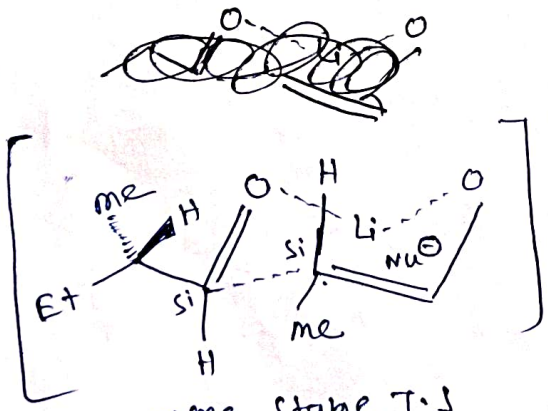
Re-Re combination



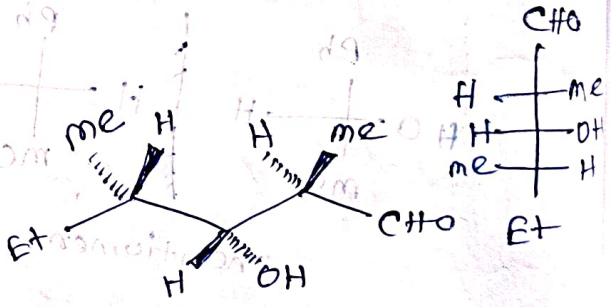
Si-Si combination more stable.

Enantiomeric T.S of equal energy and leads to major recimic mixture of two enantiomers.

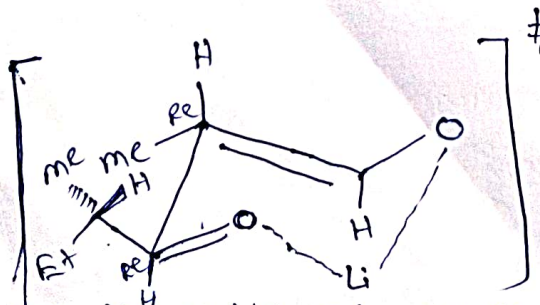
- Diastereomeric T.S of different energy & leads to diastereomeric ratio > 0 but here we do not get ee i.e ~~ee~~ e.e = 0 here



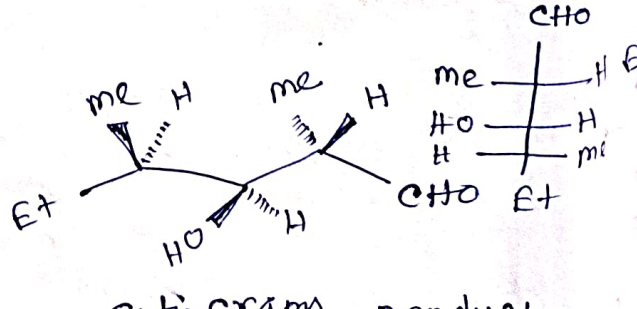
more stable T.S



Crams product.



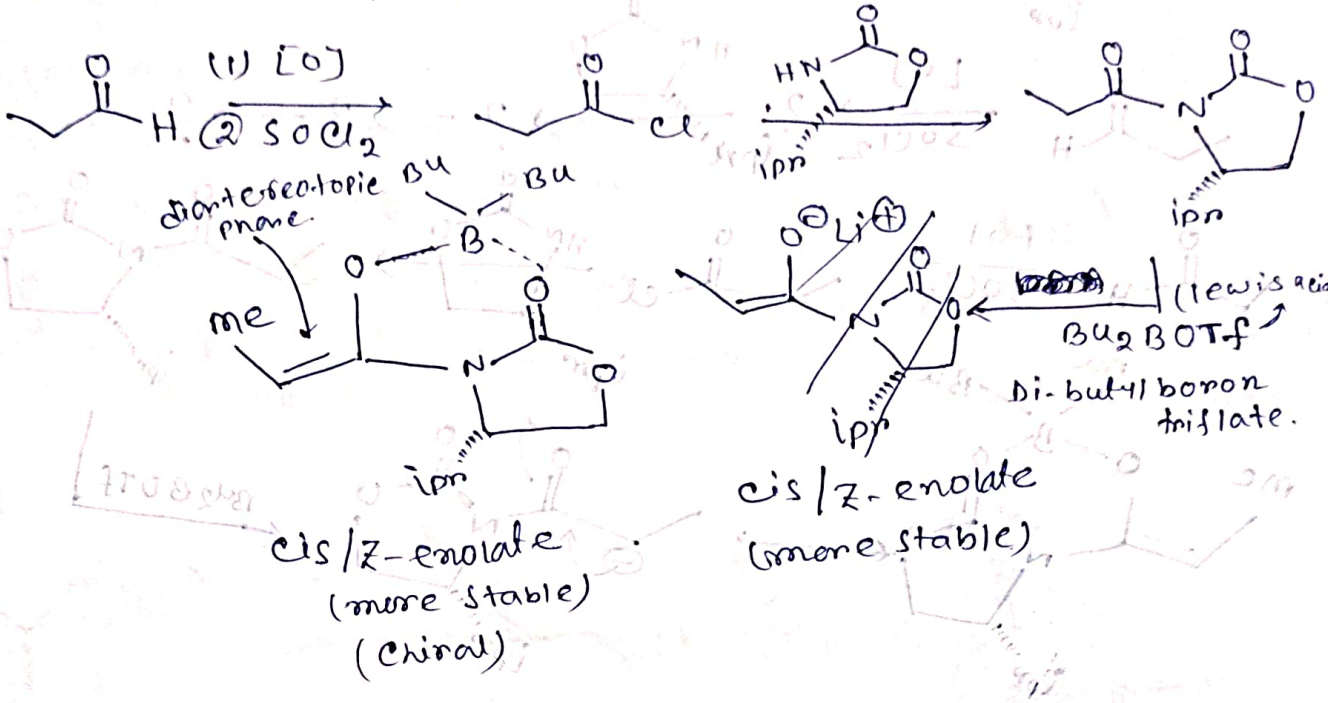
less stable T.S → Re-Re combination

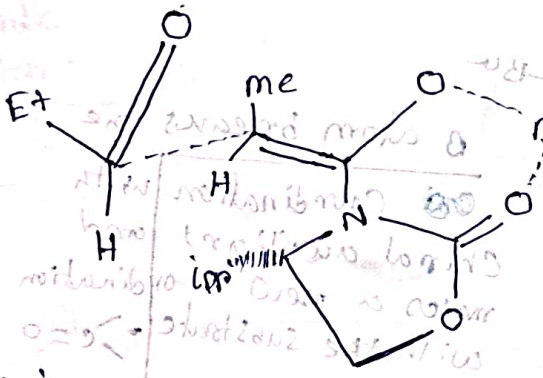


Anti-Crams product.

Asymmetric aldol

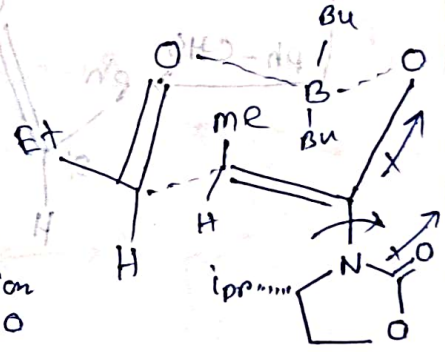
1. Achiral enolate + Chiral enolate → dr > 1
2. Chiral enolate (Chiral auxiliary) + achiral substrate → ee > 0 (Evan's aldol condensation)
3. Chiral enolate + Chiral substrate → dr > 1





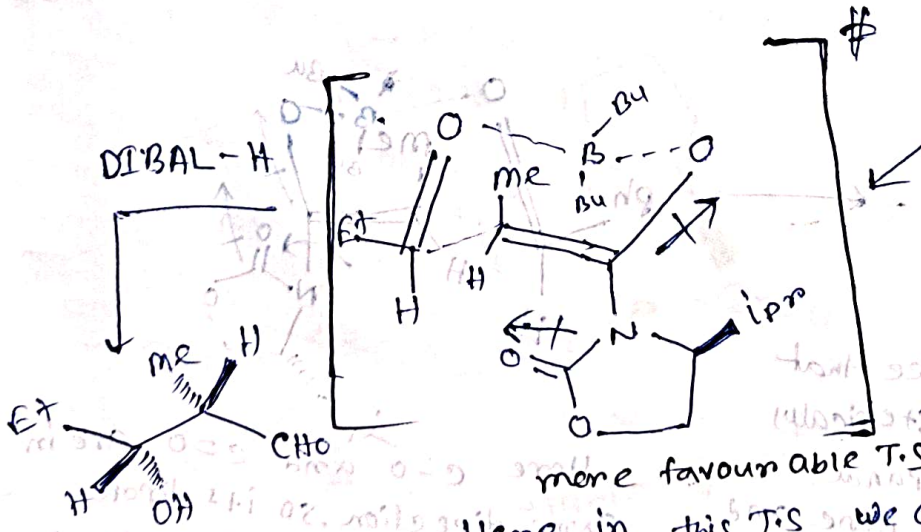
This is not an actual T.S.

B atom now breaks the coordination with Chiral auxiliary and makes new coordination with substrate ⟩C=O



This is also not the actual T.S

Here both C–O and C=O are in same direction, so its dipole moment (μ) is highest. In order to minimize the (μ) there is a free bond rotation of C–N which leads to actual more stable T.S.



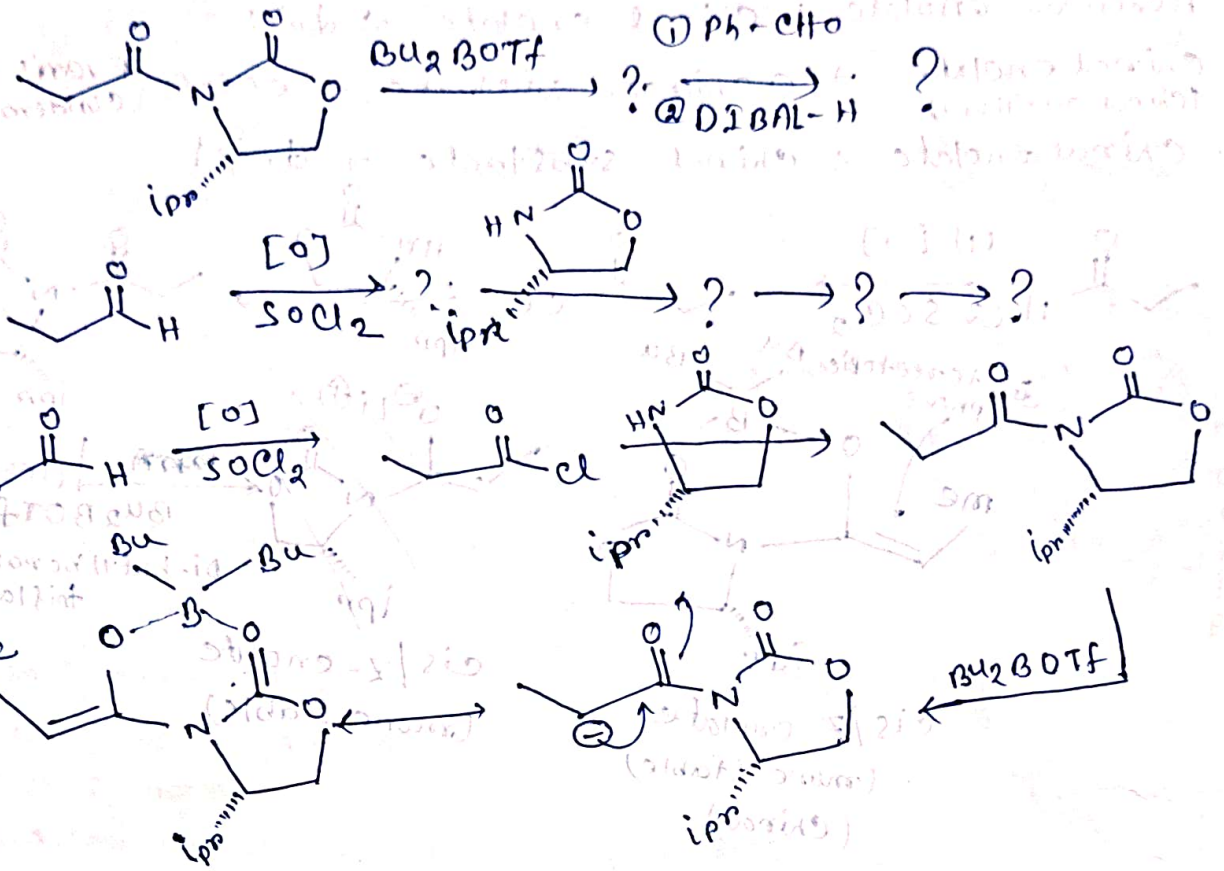
major enantiomer

Here we get ee > 0

more favourable T.S

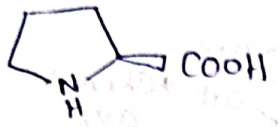
Here in this T.S we can see that Re face of enolate is sterically less hindered so propanal approaches from below the plane and leads to major enantiomer.

(8) predict the major product in reaction given below ~~and~~ with proper explanation.



Asymmetric aldol condensation using chiral catalyst

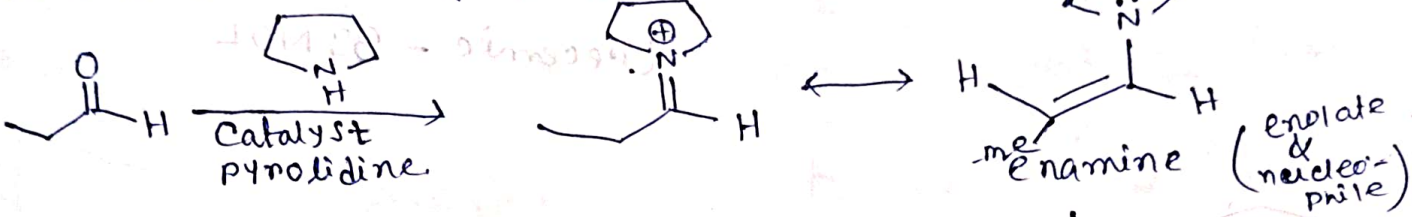
Date ⇒ 04/05/2023

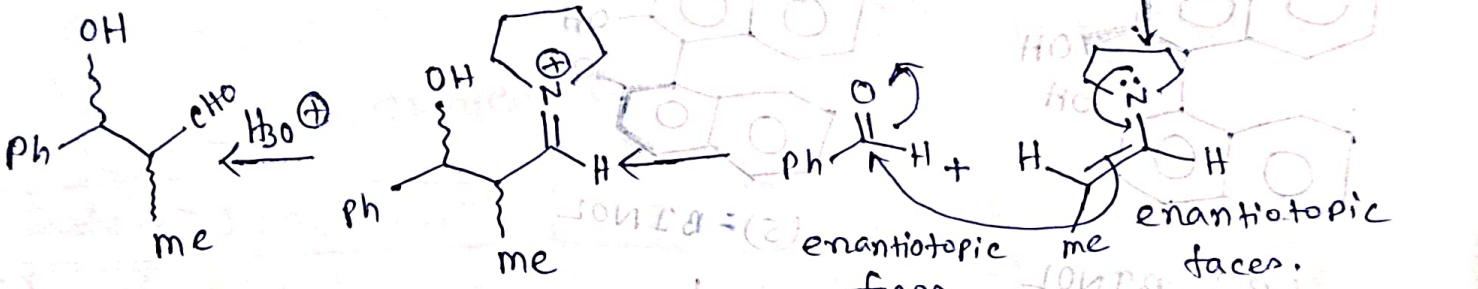


(S)-proline

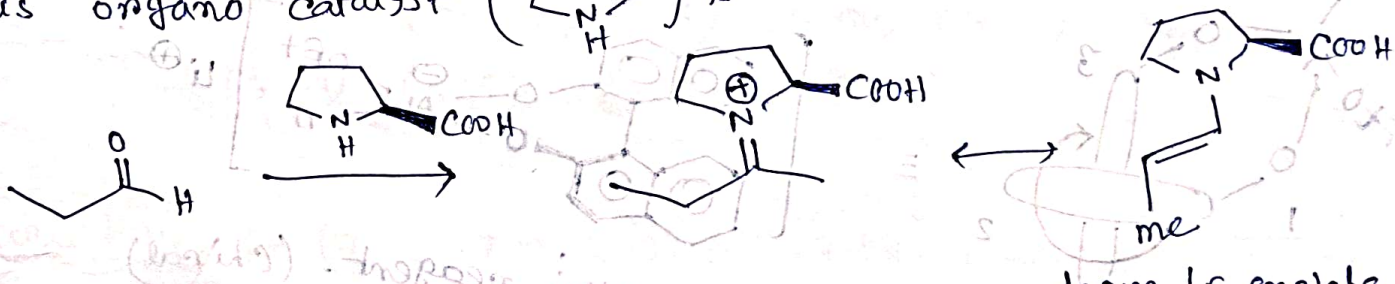
Naturally occuring amino acid

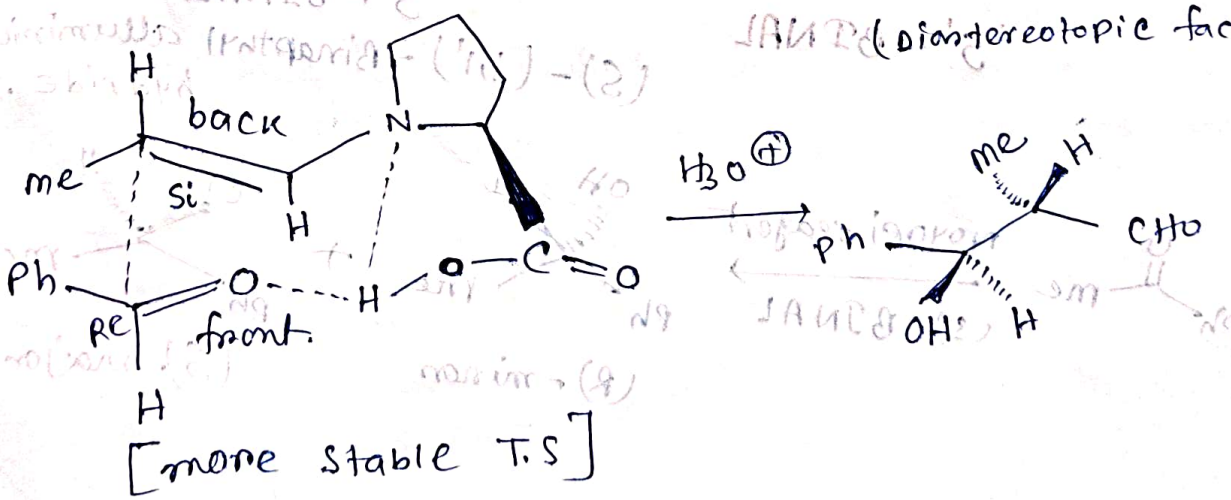
This can act as organo catalyst.





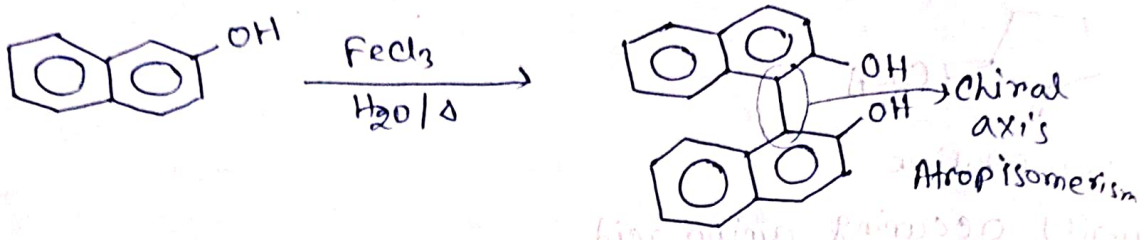
This organo catalyst ( ) is not inducing any symmetry.



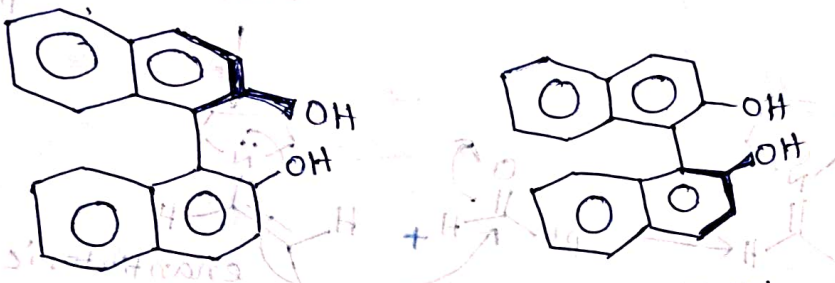


So here proline acts as an hydrogen bonding organo catalyst and induces asymmetry.

Achiral substrate + chiral reagent
(Noyori reagent / catalyst)

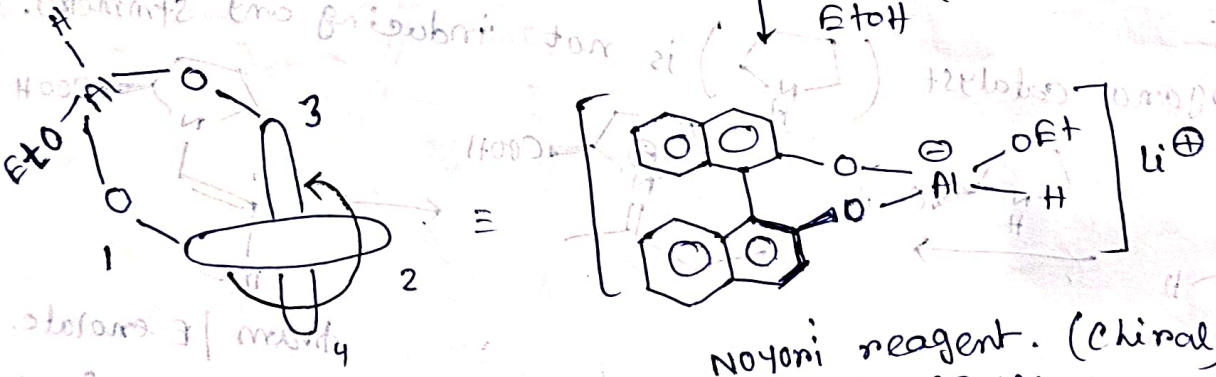


1,1'-Binaphthyl-2,2'-diol
(racemic-BINOL



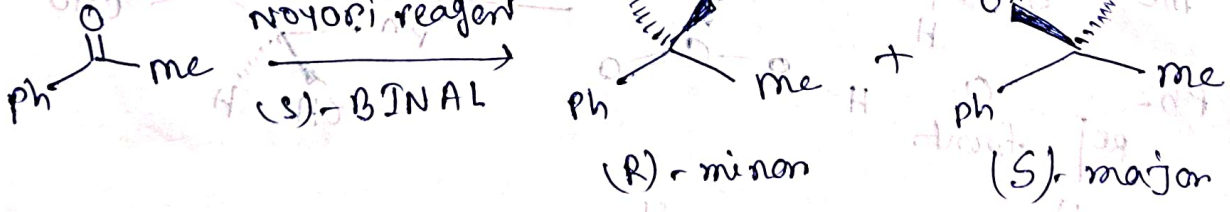
(R)-BINOL (S)-BINOL

LiAlH4 (achiral)
EtOH

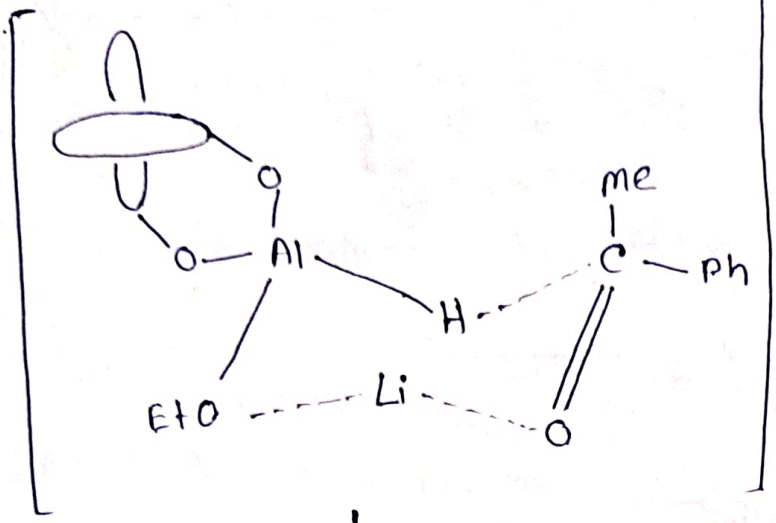


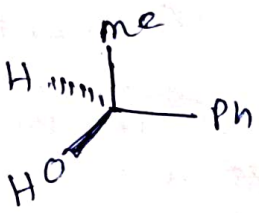
'S'-BINAL

Noyori reagent. (Chiral)
S-BINAL
(S)-(1,1')-Binaphthyl alluminium hydride.



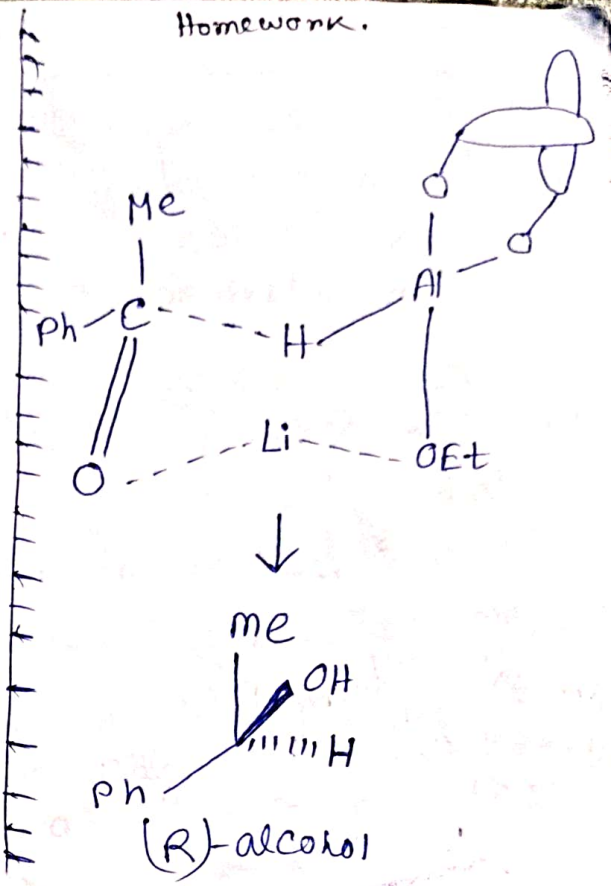
(R)-minor (S)-major





(S) alcohol

Homework.



(R)-alcohol

Date ⇒ 01/06/2023 William Carruthers

① **Oxidation** (6.1), (6.5), (6.10), (6.11), (6.15), (6.16), (6.18), (6.23), (6.25), (6.28), (6.31), (6.34), (6.35), (6.40), (6.44), (6.45), (6.50), (6.51), (6.55) (6.61), (6.63) (page 482)

Reduction :- (7.3), 7.10, 7.13, 7.23, 7.27, 7.28, 7.30, 7.46, 7.47, 7.48, 7.60, 7.62, 7.66, 7.98

Exercise, 7, 10, 11